REMARKS

Applicants acknowledge that the Examiner has withdrawn the finality of the February 8, 2002 Office Action.

Applicants acknowledge with appreciation the Examiner's statement that claims 38, 4-12, 15, 24 and 25 would be allowable if rewritten or amended to overcome the rejections under 35 U.S.C. § 112, second paragraph. Applicants further acknowledge the Examiner's statement that claims 46-48, 62, 64 and 66 are allowed.

Applicants have amended claim 24 to correct an inadvertent typographical error. Specifically, applicants have amended compound #406 in claim 24 to recite the substituent "-CH_3". Support for this amendment appears, e.g., in the specification as filed at page 51.

Applicants have deleted claims 30 and 32 and have amended claims 26, 63, 65, and 67 to delete reference to "proliferative disorders" and "viral diseases". Applicants make this amendment solely to expedite prosecution and reserve the right to pursue any cancelled subject matter in applications claiming benefit herefrom.

Applicants have amended claim 38 for clarity and to correct an inadvertent typographical error. Specifically, applicants have amended the fifth substituent in radical X to recite "-$S(O_2)$-$N(R^2)$-". Support for this amendment appears, e.g., in claims 1 and 3 as originally filed.

None of these amendments adds new matter.

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The Rejections

35 U.S.C. § 112, First Paragraph

Claims 26-37, 63, 65 and 67 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement. Specifically, the Examiner contends that the specification, while being enabling for most of the diseases listed in claim 26, does not reasonably provide enablement for treating inflammatory diseases, autoimmune diseases, viral diseases, infectious diseases, proliferative diseases, neurodegenerative diseases, and autoimmune diseases.

The Examiner contends that even though applicants have provided biological assays for testing the activity of the compounds, and have further confirmed the p38 inhibitory activity of the compounds through the Declaration of Dr. Bemis, there is no correlation providing how p38 inhibitory effect is useful in treating the "myriad diseases" recited in the claims. The Examiner further contends that it is "inconceivable" how the claimed single class of compounds can treat the list of diseases recited having diverse mechanisms.

More specifically, the Examiner contends that enablement for treating "inflammatory diseases," "autoimmune diseases," "neurodegenerative diseases," "viral diseases", "infectious diseases," and "proliferative disorders" is lacking because these diseases have different etiologies and diverse mechanisms. Applicants traverse.

To expedite prosecution, applicants have cancelled claims 30 and 32 and have amended claims 26, 63, 65, and 67 to delete several diseases that the Examiner

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contends are not enabled. Amended claims 26-29, 31, 33-37, 63, 65, and 67 are fully enabled by the evidence of record for the following reasons.

First, applicants disagree that because these diseases have different mechanisms of action they cannot all be treated by administration of the p38 inhibitors according to the present invention. These diseases are all mediated by cytokines and other inflammatory proteins which are in turn mediated by p38. Specifically, the specification as filed discloses that inhibiting p38 kinase leads to a blockade of the production of IL-1 and TNF. IL-1 and TNF, in turn, stimulate the production of cytokines such as IL-6 and IL-8 (specification page 2, lines 3-9). Thus, inhibiting p38 would lead to a blockade of production of IL-1, TNF, IL-6 and IL-8 and other pro-inflammatory proteins. IL-1, TNF, IL-6, and IL-8 are all involved in various inflammatory and immune responses. As will be discussed in more detail below, the diversity of actions of p38 kinase gives rise to a broad range of applications for the p38 inhibitors of the present invention. As disclosed in the specification as filed, p38 has been implicated in a broad array of disease states and target organs.

Second, the documents discussed below establish a link between p38 and inflammatory diseases, autoimmune diseases, and infectious diseases, and confirm that applicants' claims as filed were enabled. Applicants will also establish a link between p38 and several specific diseases, namely, rheumatoid arthritis, Crohn's disease, burn-mediated cardiac dysfunction, cardiac hypertrophy, congestive heart failure, pulmonary inflammation, and ischemia. Therefore, applicants are entitled to a generic claim directed to the treatment

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of inflammatory diseases, autoimmune diseases, neurodegenerative diseases and infectious diseases.

More specifically, Suzuki has confirmed a link between p38 and the inflammatory cytokines IL-6 and IL-8.[1] Suzuki showed that treatment of rheumatoid synovial fibroblasts with a p38 inhibitor led to specific suppression of IL-6 and IL-8 production, thereby demonstrating that "p38 MAP kinase is involved in the induction of inflammatory cytokines" (Suzuki, p. 26). Accordingly, p38 inhibitors may be effective for the treatment of rheumatoid arthritis and other inflammatory and autoimmune diseases in which inflammatory cytokines play a crucial role.

Badger I also demonstrates that inhibition of p38 inhibits production of inflammatory cytokines.[2] Specifically, Badger I supports a correlation between inhibition of p38 and inhibition of the pro-inflammatory protein TNF-α (Badger I, p. 1455). Badger I reports the efficacy of a p38 inhibitor in a variety of TNF-α-mediated animal models of inflammatory diseases that arise by both autoimmune and infectious pathways. Administration of a p38 inhibitor reduced joint edema by 72 and 45% in the mouse collagen-induced arthritis model; reduced paw inflammation in the rat adjuvant arthritis

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[1] Suzuki, M. et al., "The Role of p38 Mitogen-Activated Protein Kinase in IL-6 and IL-8 Production from the TNF-α- or IL-1β-stimulated Rheumatoid Synovial Fibroblasts," FEBS Letters, 465, pp. 23-27 (2000) ("Suzuki", Exhibit 2).

[2] Badger, A.M. et al., "Pharmacological Profile of SB 203580, a Selective Inhibitor of Cytokine Suppressive Binding Protein/p38 Kinase, in Animal Models of Arthritis, Bone Resorption, Endotoxin Shock and Immune Function," J. Pharmacol. Exp. Ther., 279, pp. 1453-1461 (1996) ("Badger I", Exhibit 3).

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model; inhibited bone resorption in the fetal rat long bone assay; and improved mouse survival in a model of endotoxin-induced shock (Badger I, p. 1459-60).

Badger II further supports the link between p38 and inflammatory cytokine synthesis.[3] As discussed in Badger II, "inhibition of p38 MAP kinase and subsequent inhibition of the synthesis of a number of important proinflammatory proteins has been identified as the primary mechanism contributing to the antiinflammatory activity of [p38 inhibitors]" (Badger II, p. 181). Importantly, the p38 pathway is "commonly associated with the early stages of host response to injury and infection" (Badger II, p. 181). Badger II observed significant antiinflammatory activity in an aggressive arthritis model of Lewis rats treated either prophylactically or therapeutically with a p38 inhibitor. Rats treated at 60 mg/kg showed 73% inhibition of paw edema and 53% normalization of bone mineral density (Badger II, p. 182). A p38 inhibitor has thus been demonstrated to have antiinflammatory effects and to protect against bone damage (Badger II, p. 182).

Humans with Crohn's Disease ("CD") have responded favorably to treatment with a p38 inhibitor in a clinical trial reported by Hommes.[4] CD is a chronic inflammatory disease that arises via an autoimmune response (Hommes, p. 7). Hommes treated 12 patients suffering from moderate to severe CD with a p38 inhibitor and reported a corresponding decrease in TNF-α production in addition to significant clinical effects

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[3] Badger, A.M. et al., "Disease-Modifying Activity of SB 242235, a Selective Inhibitor of p38 Mitogen-Activated Protein Kinase, in Rat Adjuvant-Induced Arthritis," Arthritis Rheum., 43, pp. 175-183 (2000) ("Badger II", Exhibit 4).

[4] Hommes, D. et al., "Inhibition of Stress-Activated MAP Kinases Induces Clinical Improvement in Moderate to Severe Crohn's Disease," Gastroenterology, 122, pp. 7-14 (2002) ("Hommes", Exhibit 5).

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(Hommes, p. 13). Thus, a correlation between p38 inhibition and the treatment of inflammatory and autoimmune diseases, including CD, has been demonstrated.

Ballard-Croft further supports the finding that p38 acts through the activation of inflammatory cytokines such as TNF-α.[5] Specifically, Ballard-Croft have linked p38 inhibition to the inhibition of cardiomyocyte secretion of TNF-α and the prevention of burn-mediated cardiac dysfunction (Ballard-Croft, p. H1978). These findings indicate that administration of a p38 inhibitor interrupts postburn inflammation by targeting cardiac myocytes (Ballard-Croft, p. H1978).

Shimamoto has confirmed a correlation between p38, IL-1 and cardiac hypertrophy and congestive heart failure.[6] As discussed in Shimamoto, treatment of Dahl salt-sensitive rats with a p38 inhibitor "suppressed IL-1β production" and "prevented progression of cardiac hypertrophy and congestive heart failure" (Shimamoto, p. 1415).

The antiinflammatory effects of p38 have also been shown to occur in the absence of generalized immunosupression, where, for example, p38 exerts an effect on inflammatory cytokines via a signal transduction pathway. Nick[7] showed that administration of a p38 inhibitor modulated neutrophil influx in pulmonary inflammation

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[5] Ballard-Croft, C. et al., "Role of p38 Mitogen-Activated Protein Kinase in Cardiac Myocyte Secretion of the Inflammatory Cytokine TNF-α," Am. J. Physiol. Heart Circ. Physiol., 280, pp. H1970-H1981 (2001) ("Ballard-Croft," Exhibit 6).

[6] Shimamoto, A. et al., "Inhibition of p38 Mitogen-Activated Protein Kinase Suppresses Interluekin-1β-Expression and Prevents Progression of Cardiac Hypertrophy and Congestive Heart Failure in Rats" ("Shimamoto", Exhibit 7).

[7] Nick, J.A. et al., "Role of p38 Mitogen-Activated Protein Kinase in a Murine Model of Pulmonary Inflammation," J. Immunol., 164, pp. 2151-2159 (2000) ("Nick", Exhibit 8).

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(Nick, p. 2159). Specifically, inhibition of p38 in a murine model of LPS-induced lung inflammation resulted in a loss of neutrophil migration due to a reduced neutrophil chemotaxic response (Nick, p. 2158).

p38 may also attenuate this signaling cascade in addition to its inflammatory effects. Legos has shown a p38 inhibitor to exhibit a neuroprotective effect through direct effects on ischemic brain cells.[8] p38 is present in the brain "in a wide variety of cell types including neurons, astrocytes, endothelial cells and leukocytes" (Legos, p. 74). p38 activation in the brain is an early response to the cellular stresses of severe focal ischemia, focal stroke, and myocardial/ischemia reperfusion injury (Legos, p. 75). Legos demonstrates that spontaneously hypertensive rats treated with 15 mg/kg of a p38 inhibitor 1 hour pre- and 6 hours post-middle cerebral artery occlusion showed significant neuroprotection, including behavioral improvements and a 48% reduction in infarct volume (Legos, p. 73). Thus, Legos supports a correlation between p38 and neurodegenerative diseases.

Barancik further supports the finding that inhibition of p38 protects against ischemic injury.[9] As discussed in Barancik, "p38-MAPK is part of a pathway accelerating cell death" (Barancik, pp. 481-482). Administration of a p38-specific inhibitor before and during myocardial ischemia protected pig myocardium against ischemic cell death

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[8] Legos, J.J. et al., "SB 239063, a Novel p38 Inhibitor, Attenuates Early Neuronal Injury Following Ischemia," Brain Research, 892, pp. 70-77 (2001) ("Legos", Exhibit 9).

[9] Barancik, M. et al., "Inhibition of the Cardiac p38-MAPK Pathway by SB203580 Delays Ischemic Cell Death," J. Cardiovasc. Pharmacol., 35, pp. 474-484 (2000) ("Barancik", Exhibit 10).

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(Barancik, p. 480). Therefore, Barancik further supports the action of p38 via a signaling cascade rather than through inflammatory effects.

Thus, the prior art has established a link between p38 and inflammatory conditions, autoimmune disease, infectious diseases, and neurodegenerative diseases via diverse mechanisms. The prior art also demonstrates that p38 inhibition has in vivo effects in animals, including humans, against the diseases recited in amended claims 26-29, 31, 33-37, 63, 65, and 67.

In view of the teachings of the specification and the knowledge in the art at the time this application was filed, the skilled artisan would be able to practice the claimed methods without undue experimentation and would expect that the claimed methods have the asserted utility. Accordingly, the claimed methods pass the muster of Section 112, first paragraph.

For all of the above reasons, applicants request that the Examiner withdraw these Section 112, first paragraph rejections.

35 U.S.C. § 112, Second Paragraph

Claims 4-12, 15, and 24-38 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Applicants address each of the Examiner's specific contentions below.

1. The Examiner contends that the term "comprises" in the definition of heterocyclic ring in claim 38 causes the claim to be broader than the invention. The Examiner states that applicants should replace the term "comprises" with "consists of." To

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expedite prosecution, applicants have amended claim 38 as suggested by the Examiner, thus obviating this aspect of the rejections.

2. The Examiner contends that the structural formula of compound #406 in claim 24 is incomplete because it recites "CH" rather than "CH_3" at the 4-position of the phenyl ring. Applicants have amended compound #406 to recite "CH_3", thus obviating this aspect of the rejections.

Applicants therefore request that the Examiner withdraw these Section 112, second paragraph rejections.

Conclusion

Applicants request that the Examiner consider the foregoing remarks and allow the pending claims to pass to issue. If the Examiner believes that a telephonic interview would be helpful, he is invited to call applicants' undersigned representative at any time.

Respectfully submitted,

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